(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 908 179 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
14.04.1999 Bulletin 1999/15

(51) Int. Cl.[6]: **A61K 31/07**, A61K 31/20

(21) Application number: **97114651.9**

(22) Date of filing: **23.08.1997**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV RO SI

(71) Applicants:
- **Bollag, Werner**
  4054 Basel (CH)
- **Ott, Fritz**
  8942 Oberrieden (CH)

(72) Inventors:
- **Bollag, Werner**
  4054 Basel (CH)
- **Ott, Fritz**
  8942 Oberrieden (CH)

(74) Representative:
Kjellsaa-Berger, Hanny, Dr.
F.Hoffmann-La Roche AG
Patent Department (PLP),
124 Grenzacherstrasse
4070 Basel (CH)

(54) Treatment of cell-mediated immune diseases

(57) 9-cis retinoic acid and pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, 9-cis retinal and pharmaceutically acceptable acetals thereof, and 9-cis retinol and pharmaceutically acceptable hydrolyzable esters thereof have been found to be efficacious in treating T-helper cell type 1 mediated immune diseases in well tolerated doses. Preferably, the active ingredient is formulated as a medicament for oral or topical administration.

EP 0 908 179 A1

Description

[0001] The present invention relates to the use of 9-cis retinoic acid and derivatives or precursors thereof for the manufacture of a medicament for the treatment of T-helper cell type 1 mediated immune diseases as well as to the use of said active substances for the treatment of such diseases.

[0002] Retinoids are a class of compounds structurally related to vitamin A, comprising natural and synthetic compounds. A series of retinoids have been found to be clinically useful in the treatment of dermatological and oncological diseases. All-trans retinoic acid is used topically for acne and photodamaged skin and orally for therapy of acute promyelocytic leukemia. Severe acne responds very well to treatment with oral 13-cis retinoic acid. Etretinate and acitretin are used for therapy of psoriasis and other keratinizing dermatoses. Furthermore, some premalignant lesions, such as actinic keratoses and oral leukoplakias respond to retinoids. Retinoids have also been found to be effective in the prevention of cancer e.g. in prevention of second primary tumors in patients with carcinomas of head and neck.

[0003] Experimentally, retinoids have an influence on cell proliferation, cell differentiation, apoptosis, angiogenesis, keratinization, sebum secretion, photodamaged skin, morphogenesis and immune reactions.

[0004] The activity of retinoids is thought to be mediated by the nuclear retinoid receptors, belonging to the superfamily of steroid, thyroid and vitamin D receptors. Two subtypes of nuclear retinoid receptors are known, the retinoic acid receptors RARs α, β, γ and the retinoid X receptors RXRs α, β, γ. All-trans retinoic acid binds and activates RARs, but not RXRs. 9-cis retinoic acid binds and activates RXRs, in addition to RARs [Levine et al., Nature 355, 359-361 (1992); Heyman et al., Cell 68, 397-406 (1992); WO-A-93/11755].

[0005] Oral administration of 9-cis retinoic acid is efficacious in the treatment of acute promyelocytic leukemia [Miller et al., Blood 85, 3021-3027 (1995)]. Topical administration of 9-cis retinoic acid is effective in the treatment of AIDS-related Kaposi's sarcoma [Duvic et al., Proc. Amer. Soc. Clin. Oncol. 16, 46a (1997)]. In a series of solid tumors no major objective regression was observed with oral 9-cis retinoic acid therapy [Kurie et al., Clin. Cancer Res. 2, 287-293 (1996); Miller et al., Clin. Cancer Res. 2, 471-475 (1996)]. WO-A-93/11755 further showed that 9-cis retinoic acid inhibits the morphological differentiation of NHEK534 cells (epidermal keratinocytes) and suggested in vivo modulation of skin-related processes such as acne, aging, and wrinkling with 9-cis retinoic acid or related compounds. In contrast to 13-cis retinoic acid, oral administration of 9-cis retinoic acid had however no therapeutic activity in acne patients [Ott et al., Dermatology 193, 124-126 (1996)].

[0006] In vitro and in vivo experimental investigations have shown that certain retinoids have immunomodulatory properties [Shapiro et al., in: Saurat, ed, Retinoids, New Trends in Research and Therapy, Karger, Basel, pp. 225-235 (1985); Ross et al., in: Sporn et al., eds, The Retinoids. Biology, Chemistry, and Medicine, 2nd edition, Raven Press, New York, pp. 521-543 (1994); Racke et al., J. Immunol. 154, 450-458 (1995); Cantorna et al., J. Immunol. 156, 2674-2679 (1996); Cantorna et al., J. Immunol. 152, 1515-1522 (1994); Cantorna et al., Eur. J. Immunol. 25, 1673-1679 (1995); Massacesi et al., J. Clin. Invest. 88, 1331-1337 (1991); Brinckerhoff et al., Science 221, 756-758 (1983)].

[0007] However, despite intensive clinical research with retinoids in the last 27 years, retinoids have not been reported to be clinically useful in the therapy of immunologically mediated diseases. Neither diseases caused by T-helper type-1 cell (Th1) dependent cellular immunity, nor diseases caused by T-helper type-2 cell (Th2) dependent humoral immunity, have been reported to respond to retinoids. As to the classification into Th1 dependent diseases - such as autoimmune and other cell-mediated immune diseases, e.g. rheumatoid arthritis, multiple sclerosis, uveoretinitis, thyreoiditis, insulin dependent diabetes mellitus, eczema and systemic lupus erythematosus, as well as rejection of allogeneic organ transplants - and Th2 dependent diseases - i.e. diseases with dominant humoral or antibody-mediated diseases such as allergic disorders, e.g. atopic dermatitis, allergic rhinitis, hay fever and allergic bronchial asthma - reference is made to Romagnani, ed, Th 1 and Th 2 Cells in Health and Disease. Chem. Immunol., Karger, Basel, 63, pp. 158-170 and 187-203 (1996).

[0008] For the first time, quite unexpectedly, it has now been found that a retinoid - namely 9-cis retinoic acid as well as its salts, its esters and its metabolic precursors or prodrugs - is clinically efficacious in the therapy of Th1 dependent diseases.

[0009] In the scope of the present invention the term „metabolic precursors and prodrugs" encompasses compounds that are converted metabolically into 9-cis retinoic acid, and it includes, in particular, 9-cis retinal and 9-cis retinol as well as pharmaceutically acceptable acetals of 9-cis retinal and pharmaceutically acceptable hydrolyzable esters of 9-cis retinol.

[0010] In accordance with this invention, it has thus been found that that administration of 9-cis retinoic acid, its pharmaceutically acceptable salts, its pharmaceutically acceptable hydrolyzable esters, 9-cis retinal, its pharmaceutically acceptable acetals, 9-cis retinol and its pharmaceutically acceptable hydrolyzable esters, are efficaceous in treating patients with T-helper cell type 1 (Th1) mediated diseases.

[0011] The invention therefore relates to the use of 9-cis retinoic acid, a pharmaceutically acceptable salt or a pharmaceutically acceptable hydrolyzable ester thereof, 9-cis retinal or a pharmaceutically acceptable acetal thereof or 9-cis retinol or a pharmaceutically acceptable hydrolyzable ester thereof for the manufacture of a medicament for the

treatment of T-helper cell type 1 (Th1) mediated immune diseases.

[0012] The invention also relates to a method for treating patients having T-helper cell type 1 (Th1) mediated immune diseases comprising administering to said human patient a compound selected from the group consisting of 9-cis retinoic acid, pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, 9-cis retinal and pharmaceutically acceptable acetals thereof as well as 9-cis retinol and pharmaceutically acceptable hydrolyzable esters thereof said compound being administered in an amount effective to treat said disease.

[0013] In the scope of the present invention, the term „T-helper cell type 1 mediated immune diseases" relates to diseases with dominant cellular immune response, and it encompasses, in particular, autoimmune and other cell-mediated immune diseases, such as rheumatoid arthritis, multiple sclerosis, uveoretinitis, thyreoiditis, insulin dependent diabetes mellitus, eczema, systemic lupus erythematosus and allogeneic graft rejection (e.g. rejection of allogeneic skin, kidney, heart, liver or lung transplants). The term „eczema" relates, in particular, to eczema due to delayed type hypersensitivity. The term „treatment" or „treating" includes preventive and/or therapeutic treatments.

[0014] 9-cis retinoic acid and its derivatives and metabolic precursors and prodrugs when administered to patients are effective, in particular in the therapy of the following T-helper cell type 1 (Th1) mediated diseases: rheumatoid arthritis, multiple sclerosis, uveoretinitis, thyreoiditis, insulin dependent diabetes mellitus, systemic lupus erythematosus as well as eczema with its various classes of exogenous eczema, such as irritant dermatitis and allergic contact dermatitis, endogenous eczema, such as seborrhoic dermatitis, asteatotic eczema and discoid eczema, and eczemas localised at various sites of the body. 9-cis retinoic acid and its derivatives and metabolic precursors and prodrugs are effective in all those immune diseases which might be somehow linked with an increase of Th1 cell activity and an increased secretion of the related cytokines interleukin-12, interleukin-2, interferon γ and tumor necrosis factor α, β.

[0015] For the treatment given above, the active compound, i.e. 9-cis retinoic acid, a pharmaceutically acceptable salt or a pharmaceutically acceptable hydrolyzable ester thereof, 9-cis retinal or a pharmaceutically acceptable acetal thereof or 9-cis retinol or a pharmaceutically acceptable hydrolyzable ester thereof, is administered either systemically or topically. Preferably, said compound is administered as a composition containing said active compound and a pharmaceutically acceptable carrier or diluent compatible with said active compound. In preparing such composition, any conventional pharmaceutically acceptable carrier can be utilized. When the drug is administered orally, it is generally administered at regular intervals, conveniently at mealtimes or once daily. It has been established that this compound is effective in doses which show no or only mild side effects when given orally or when given topically. Therefore, oral administration of the active compound is generally preferred. For treating eczema however topical administration may also be used advantageously.

[0016] In the treatment of T-helper cell type 1 mediated immune diseases, 9-cis retinoic acid and its derivatives and metabolic precursors and prodrugs, when administered orally, are therapeutically efficacious in doses which induce no adverse events or only such mild side effect as dry lips. All retinoids exerting therapeutic effects in dermatological and oncological indications have to be administered orally in doses which induce more or less marked side effects, belonging to the toxic syndrome of hypervitaminosis A, such as mucocutaneous, musculoskeletal and neurologic manifestations, particularly headache. In addition, they produce laboratory abnormalities such as elevated transaminases (ALAT, ASAT), elevated alkaline phosphatase, as well as elevated triglycerides and cholesterol. In contrast, the daily doses of 9-cis retinoic acid and its derivatives and metabolic precursors and prodrugs (typically 20 to 60 mg) therapeutically efficacious in T-helper cell type 1 mediated immune diseases produce only very slight side effects, such as dry lips, whereas all the other toxic signs and symptoms of the hypervitaminosis A syndrome, including the laboratory abnormalities, were not induced.

[0017] These same low daily doses of 9-cis retinoic acid, however, had no therapeutic effect on non-malignant skin-disorders, such as acne, psoriasis, lamellar ichthyosis, Darier's disease and lichen planus. In summary, it was found that the very well tolerated low daily doses of 20 to 60 mg of 9-cis retinoic acid (and its derivatives and metabolic precursors and prodrugs) are efficacious in the treatment of T-helper cell type 1 mediated immune diseases, whereas such doses are not efficacious in the treatment of non-malignant skin disorders, such as acne, psoriasis and other keratinizing dermatoses. In malignant skin diseases and solid tumors of other organs, even high oral daily doses of 9-cis retinoic acid of up to 300 mg, inducing marked to severe side effects, did not lead to major objective tumor regressions.

[0018] In the treatment of T-helper cell type 1 mediated immune diseases, 9-cis retinoic acid, a pharmaceutically acceptable salt or a pharmaceutically acceptable hydrolyzable ester thereof, 9-cis retinal or a pharmaceutically acceptable acetal thereof or 9-cis retinol or a pharmaceutically acceptable hydrolyzable ester thereof can be used alone or in combination with other measures, e.g. in combination with other pharmaceutically active substances such as topical or systemic corticosteroids and other immunosuppressive agents (cytostatics, antimetabolites, biological response modifiers, e.g. interferons, interleukins and other cytokines). If used in combination with other substances, 9-cis retinoic acid or its derivative or metabolic precursor or prodrug and said other substance can be administered separately or, preferably, incorporated in effective amounts into one pharmaceutical composition.

[0019] In the scope of the present invention, the „pharmaceutically acceptable salts" includes any salt chemically permissible in the art for 9-cis-retinoic acid and applicable to human patients in a pharmaceutically acceptable preparation.

Any such conventional pharmaceutically acceptable salt of 9-cis retinoic acid can be utilized. Among the conventional salts which can be utilized there are the base salts included, for example, alkali metal salts such as the sodium or potassium salt, alkaline earth metal salts such as the calcium or magnesium salt, and ammonium or alkyl ammonium salts.

[0020] In accordance with this invention the 9-cis retinoic acid can also be administered in the form of its pharmaceutically acceptable hydrolyzable esters. Any pharmaceutically acceptable hydrolyzable ester can be used in the compositions and methods of this invention. Among the preferred esters are: the aromatic esters such as benzyl esters in which the benzyl moiety is unsubstituted or substituted with lower alkyl, halo, nitro, thio, or substituted thio; or lower alkyl esters, e.g. ethyl, t-butyl, cyclopentyl, cyclohexyl or cycloheptyl ester; or 9-fluorenylmethyl ester.

[0021] In the scope of the present invention the term „alkyl" means straight-chain, branched or cyclic alkyl residues, in particular those containing from 1 to 12 carbon atoms, such as methyl, ethyl, propyl, isopropyl, t-butyl, decyl, dodecyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term „lower alkyl" means alkyl groups containing from 1 to 7 carbon atoms.

[0022] In accordance with this invention a metabolic precursor or prodrug of 9-cis retinoic acid, in particular, 9-cis retinal, 9-cis retinol, a pharmaceutically acceptable acetal of 9-cis retinal or a pharmaceutically acceptable hydrolyzable esters of 9-cis retinol can alternatively be used instead of 9-cis retinoic acid. Any pharmaceutically acceptable acetal of 9-cis retinal and any pharmaceutically acceptable hydrolyzable ester of 9-cis retinol can be used in the compositions and methods of this invention. Among the preferred acetals of retinal are dialkyl acetals, especially di(lower alkyl) acetals such as the diethyl acetal, and dibenzyl acetals, wherein the benzyl moieties are unsubstituted or substituted with lower alkyl, halo, nitro, thio or substituted thio. Among the preferred hydrolyzable esters of 9-cis retinol are the esters formed with C_1-C_{20}-carboxylic acids such as C_1-C_{20}-alkanoic acids and C_1-C_{20}-alkenoic acids; particularly preferred are those carboxylic acid esters which contain and even number of carbon atoms in the carboxylic acid moiety such as acetate, stearate or palmitate.

[0023] The aforementioned 9-cis retinoic acid and its salts, its esters and its metabolic precursors or prodrugs are useful especially in pharmaceutically acceptable oral or topical modes. These pharmaceutical compositions contain said active compound in association with a compatible pharmaceutically acceptable carrier material. Any conventional carrier material can be utilized. The carrier material can be an organic or inorganic inert carrier material suitable for oral administration. Suitable carriers include water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene-glycols, petroleum jelly and the like. Furthermore, the pharmaceutically active preparations may contain other pharmaceutically active agents. Additionally, additives such as flavouring agents, preservatives, stabilizers, emulsifying agents, buffers and the like may be added in accordance with accepted practices of pharmaceutical compounding.

[0024] The pharmaceutical preparations can be made up in any conventional form including inter alia: (a) a solid form for oral administration such as tablets, capsules (e.g. hard or soft gelatine capsules), pills, sachets, powders, granules, and the like; and (b) preparations for topical administrations such as solutions, suspensions, ointments, creams, gels, micronized powders, aerosols and the like. The pharmaceutical preparations may be sterilized and/or may contain adjuvants such as preservatives, stabilizers, wetting agents, emulsifiers, salts for varying the osmotic pressure and/or buffers.

[0025] For topical administration to the skin or mucous membrane the aforementioned derivative is preferably prepared as ointments, tinctures, creams, gels, solution, lotions, sprays, suspensions, shampoos, hair soaps, perfumes and the like. In fact, any conventional composition can be utilized in this invention. Among the preferred methods of applying the composition containing the agents of this invention is in the form of an ointment, cream or lotion. The pharmaceutical preparation for topical administration to the skin can be prepared by mixing the aforementioned active ingredient with non-toxic, therapeutically inert, solid or liquid carriers customarily used in such preparation. These preparations generally contain at least about 0.0005 percent by weight, preferably 0.0005 to 0.03 and more preferably about 0.001 to 0.01 percent by weight, of the active ingredient (i.e. 9-cis retinoic acid or its derivative or its metabolic precursor or prodrug) based upon the total weight of the composition. Since toxicity and irritancy of the active ingredient varies, depending on the kind of tissue - normal or pathologically altered - on which it is applied, it may however often be used in topical compositions in amounts up to 0.15 percent by weight or even higher amounts. It is also preferred to apply these preparations once or twice daily to the skin. These preparations can be applied according to the need of the patient. In carrying out this invention, the active ingredient can be applied in an aqueous solution or an alcohol solution such as ethanol.

[0026] In preparing the topical preparations described above, additives such as preservatives, thickeners, perfumes and the like conventional in the art of pharmaceutical compounding of topical preparation can be used. In addition, conventional antioxidants or mixtures of conventional antioxidants can be incorporated into the topical preparations containing the aforementioned active agent. Among the conventional antioxidants which can be utilized in these preparations are included N-methyl-α-tocopherolamine, tocopherols, butylated hydroxyanisole, butylated hydroxytoluene, ethoxyquin and the like. Cream-base pharmaceutical formulations containing the active agent, used in accordance with this invention, are composed of aqueous emulsions containing a fatty acid alcohol, semi-solid petroleum hydrocar-

bon, ethylene glykol and an emulsifying agent.

[0027] Ointment formulations containing the active agent in accordance with this invention comprise admixtures of a semi-solid petroleum hydrocarbon with a solvent dispersion of the active material. Cream compositions containing the active ingredient for use in this invention preferably comprise emulsions formed from a water phase of a humectant, a viscosity stabilizer and water, an oil phase of a fatty acid alcohol, a semi-solid petroleum hydrocarbon and an emulsifying agent and a phase containing the active agent dispersed in an aqueous stabilizer-buffer solution. Stabilizers may be added to the topical preparation. Any conventional stabilizer can be utilized in accordance with this invention. In the oil phase, fatty acid alcohol components function as a stabilizer. These fatty acid alcohol components are derived from the reduction of a long-chain saturated fatty acid containing at least about 14 carbon atoms. Also, conventional perfumes and lotions generally utilized in topical perparation for the hair can be utilized in accordance with this invention. Furthermore, if desired, conventional emulsifying agents can be utilized in the topical preparations of this invention.

[0028] A preferred oral dosage form comprises tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. Each tablet, pill, sachet or capsule can preferably contain from about 5 to about 50 mg, more preferably from about 10 to about 20 mg, of active ingredient. The oral dosages contemplated in accordance with the present invention will vary in accordance with the needs of the individual patient as determined by the prescribing physician. Generally, however, a daily dosage of from about 0.15 mg to about 1.5 mg per kg of body weight and preferably from about 0.3 mg to about 0.9 mg per kg of body weight of the patient is utilized. This dosage may be administered according to any dosage schedule determined by the physician in accordance with the requirements of the patient.

[0029] The dosage for treatment typically depends on the route of administration, the age, weight and disease condition of the individual. Suitable dosage forms are known in the art or can be easily obtained in a manner known per se. Formulations of lotions, gels, creams, hard or soft gelatin capsules, tablets and sachets that are particularly suitable in the scope of the present invention or that can be easily adjusted in accordance with the above teaching are disclosed e.g. in US-A-5,428,071.

Example 1

Activity of 9-cis retinoic acid in chronic hand eczema

a) Methods

[0030] Five patients, four men and one woman, with chronic hand eczema, refractory to conventional treatment, were treated with 9-cis retinoic acid. Their mean age was 52, range 37-83. Before the start of 9-cis retinoic acid therapy, their eczema had already lasted for 3 months to 5 years, with a mean of 27 months. Besides avoidance of irritants and allergens, their previous treatment consisted in topical emollients, topical corticosteroids (in all five patients) and additional X-rays in two patients. The patients had the following types of chronic hand eczema: 1 hyperkeratotic palmar eczema, 1 fingertip eczema, 1 discoid eczema, 1 pompholyx of palms, 1 pompholyx of palms and soles. Therapy consisted in a once daily oral dose of 40 mg 9-cis retinoic acid, given in the form of two soft gelatin capsules containing 20 mg of 9-cis retinoic acid each, with breakfast. Mean duration of treatment was 2 months, range 1-3 months. Mean total dose was 2368 mg, range 1320-3560 mg. Mean total dose per month was 1184 mg. The following lesions and symptoms were recorded on a 0-4 scale (0 = none, 1 = mild, 2 = moderate, 3 = marked, 4 = severe) and used for evaluating the therapeutic effect: Papules and vesicles, erythema, desquamation, hyperkeratosis, rhagades and pruritus. Side effects as well as time to relapse were recorded.

b) Results

[0031] As can be seen from Table 1, all five patients responded markedly to 9-cis retinoic acid (9-cis-RA) and all the various lesions and symptoms were improved by the treatment. The total lesion-symptom score of the 5 patients was reduced by a mean of 76 % (range 59-93 %). All the various lesions and symptoms were favourably influenced and regressed by 62-100 %. A relapse was recorded in all five patients 1 to 8.5 months, mean 3.4 months, after end of treatment. 9-cis retinoic acid in a dose of 40 mg daily was very well tolerated. The only side effect noted in all 5 patients was dry lips. No other mucocutaneous manifestations, no headache, seen with higher doses no musculoskeletal or other symptoms were observed. Such symptoms were seen with higher doses [Kurie et al., Clin. Cancer Res. 2, 287-293 (1996); Miller et al., Clin. Cancer Res. 2, 471-475 (1996)]. The well known laboratory abnormalities, such as elevation of transaminases (ALAT, ASAT), alkaline phosphatase, triglycerides and cholesterol, frequently caused by retinoids were not seen with this low dosage of 9-cis retinoic acid. The success of the therapy with 9-cis retinoic acid in patients with chronic hand eczema, refractory to conventional treatment, was considered as good to very good by the doctor, as well as by the patients.

Table 1

Treatment of Chronic Hand Eczema

Patient	1		2		3		4		5		Mean	
Age (years)	83		41		49		50		37		52	
Sex	f		m		m		m		m			
Duration of eczema	3 months		20 months		16 months		5 years		3 years		27 months	
Previous treatment	topical steroids		topical steroids		topical steroids, X-rays		topical steroids		topical steroids, X-rays			
Success of previous treatment	none		slight		moderate		moderate		moderate			
9-cis-RA therapy												
Oral daily dose	40 mg		40 mg		40 mg		40 mg		40 mg		40 mg	
Duration of treatment	62 days		56 days		56 days		89 days		33 days		59 days	
Efficacy (0-4 scale, before | after treatment)												
Papules, vesicles	1	0	1	0	1	0.5	1	0.5	2	0		
Pruritus	3	0	3	1	2	1	2	1	2	0		
Erythema	2	0	2	0	3	1	3	1	3	2		
Desquamation	2	1	3	1	3	1	3	1	2	1		
Hyperkeratosis	4	0	3	0	1	1	2	1	1	0		
Rhagades	3	0	2	0	1	0	0.5	0	1	0		
Total score	15	1	14	2	11	4.5	11.5	4.5	11	3	12.5	3

Table 1 (continued)

Treatment of Chronic Hand Eczema

Patient	1		2		3		4		5		Mean
Success of 9-cis RA treatment											
Doctor's assessment	very good		very good		good		good		good		
Patient's assessment	very good		very good		good		very good		very good		
Side effects* (before | after treatment)											
Headache	-	-	-	-	-	-	-	-	-	-	
Dry lips	-	+	-	+	-	+	-	+	-	+	
Other symptoms	-	-	-	-	-	-	-	-	-	-	
Laboratory abnormalities	-	-	-	-	-	-	-	-	-	-	
Time to relapse after end of treatment (months)	8.5		1.5		1		1		5		3.4

Side effects: - (none), + (mild), ++ (moderate), +++ (severe)

Claims

1. The use of a compound selected from the group consisting of 9-cis retinoic acid and pharmaceutically acceptable salts and pharmaceutically acceptable hydrolyzable esters thereof, 9-cis retinal and pharmaceutically acceptable acetals thereof, and 9-cis retinol and pharmaceutically acceptable hydrolyzable esters thereof as active ingredient for the manufacture of a medicament for the treatment of T-helper cell type 1 mediated immune diseases.

2. The use according to claim 1, wherein the active ingredient is used in combination with a pharmaceutically acceptable carrier.

3. The use according to claim 1 or 2, wherein the medicament is manufactured for oral or topical administration.

4. The use according to any one of claims 1 to 3, wherein the medicament is manufactured as a tablet, capsule, pill, sachet, ointment, cream or lotion.

5. The use according to any one of claims 1 to 4, wherein the medicament is manufactured as a tablet, capsule, pill or sachet containing 5 to 50 mg, preferably 10 to 20 mg, of active ingredient.

6. The use according to any one of claims 1 to 5, wherein the medicament is manufactured for oral daily dosage of from 0.15 mg to 1.5 mg, preferably from 0.3 mg to 0.9 mg, per kg of body weight.

7. The use according to any one of claims 1 to 4, wherein the medicament is manufactured as an ointment, cream or lotion containing 0.0005 to 0.03 percent by weight, preferably 0.001 to 0.01 percent by weight, of the active ingredient.

8. The use according to any one of claims 1 to 7, wherein the active ingredient is selected from the group consisting of 9-cis retinoic acid and alkali metal salts, alkaline earth metal salts, benzyl esters, lower alkyl esters and 9-fluorenylmethyl esters thereof, 9-cis retinal and dialkyl acetals and dibenzyl acetal thereof, and 9-cis retinol and esters therof formed with C_1-C_{20}-carboxylic acids.

9. The use according to any one of claims 1 to 8, wherein the medicament is manufactured for the treatment of autoimmune diseases, rheumatoid arthritis, multiple sclerosis, uveoretinitis, thyreoiditis, insulin dependent diabetes mellitus, eczema, systemic lupus erythematosus or allogeneic graft rejection.

10. The use according to any one of claims 1 to 9,wherein the medicament is manufactured for the treatment of exogenous eczema, such as irritant dermatitis and allergic contact dermatitis, or of endogenous eczema, such as seborrhoic dermatitis, asteatotic eczema and discoid eczema.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 11 4651

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO 94 22818 A (PFIZER) 13 October 1994 * page 4, line 13-14 *	1	A61K31/07 A61K31/20
X	EP 0 579 915 A (HOFFMANN LA ROCHE) 26 January 1994 * page 2, line 1-12 * * page 3, line 56 - page 4, line 5 *	1-10	
X	US 5 093 360 A (YU RUEY J ET AL) 3 March 1992 * column 1, line 41 - column 2, line 32 * * column 3, line 56-58 *	1-10	
X	US 5 658 949 A (AGGARWAL BHARAT B) 19 August 1997 * column 5, line 35-40; claims 2,6,15 * * column 5, line 58-61 *	1-10	
A	YILI YANG ET AL.: "9-cis-Retinoic Acid inhibits activation-driven T-cell apoptosis: Implications for Retinoid X Receptor involvement in thymocyte development" PROC. NATL. ACAD. SCI. USA, vol. 90, July 1993, pages 6170-6174, XP000578397 * abstract *	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	6 July 1998	Engl, B

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)